REMARKS/ARGUMENTS

Claims 67-71, 75, 77-79 and 95 were previously pending and have been examined. Claims 96-103 are added. Claims 26 and 76, 78 and 79 have been cancelled herein as redundant. Other claims were cancelled previously. Support for the amendment to claim 75 is provided by cancelled claim 76. Claim 75 has been amended to define zinc finger protein specificity in analogous fashion to the other independent claims. New claims 96-98 and 100-102 add elements from claims 68 to 70 to the other independent claims, claims 75 and 95. New claims 99 and 103 specify that zinc finger proteins are topically or to a specific tissue of an animal. Support for topical administration is provided at e.g., p. 64, line 18. Support for administering to a specific target tissue as recited in claim 103 is provided at e.g., p. 64, lines 26-27. Applicants respond to the Examiner's comments using the paragraph numbering of the office action.

1. Applicants note that in fact the restriction requirement was not traversed. However, as previously pointed out, applicants are entitled to examination of generic claims for proteins that modulate angiogenesis and method for methods of modulating angiogenesis on indication of allowability of the elected species.

2. The status of priority applications has been updated.

3. The Examiner says the information disclosure of December 18, 2001 is missing from the file. However, applicants believe the Examiner may be referring to the information disclosure statement filed March 11, 2002 of which no record is present in the PAIR system. An additional copy of this information disclosure statement is attached. It is unclear whether the Examiner is also missing copies of the references cited therein. If so, the Examiner is requested to obtain them from child case, USSN 10/006069, in which the same references have been cited. However, in the event the Examiner is unable to locate the references he is requested to telephone the undersigned.

4. The claims have been amended to include reference to SEQ ID NOS.

5. Rejections under 35 USC 112, second paragraph.

5a. The Examiner says that claim 26 is indefinite in that the claim does not further limit claim 67. In response, claim 26 has been cancelled. Applicants concur with the Office's statement that expression of a plurality of splice variants is inherent to expression of the VEGF gene. Applicants thus understand that the remaining claims cover modulation of expression of a plurality of splice variants of the VEGF gene and understand, unless advised to the contrary, that this is the Office's position, as well.

5b. Claims 67 and 71 are rejected as broad for reciting the term modulating on the basis that modulating includes inhibiting and stimulating. Applicants traverse. Breadth of a claim is not to be equated with indefiniteness. *In re Miller,* 169 USPQ 597 (CCPA 1971). Claims 67 and 71 are directed to the genus of modulation, of which stimulation and inhibition are species. A zinc finger protein binding within a VEGF gene can cause either stimulation or inhibition depending, for example, on the nature of the regulatory domain linked to the zinc finger protein (see specification at e.g., paragraph bridging pp. 28-29).

5c. Claim 67 has been amended to recite the acronym for VEGF.

5d. Claim 71 is said to be unclear in whether the reference to a plurality of VEGF genes means genes in the same animal or different organisms. However, claim 71depends from claim 67, which recites "introducing a zinc finger protein into *an animal*" (emphasis added). Claim 71 also recites that the plurality of VEGF genes are modulated. Because the zinc finger protein is introduced into an animal and the plurality of VEGF genes are modulated in that animal, it is clear that the reference to a plurality of VEGF genes means VEGF genes in the same animal as that to which the zinc finger protein is administered. Accordingly the meaning of claim 71 is clear.

5e. Claim 76 is rejected for not further limiting claim 75. Claim 76 has been canceled and claim 75 has been amended to specify that the animal genome comprises a VEGF gene comprising a target site to which the zinc finger protein binds.

5f. Claim 76 is rejected as unclear whether introduction of the zinc finger protein needs to be at the wound or whether systemic administration is envisaged. Applicants assume that this rejection is directed to claim 95, which is the only independent pending claim reciting treatment of a wound. Both systemic and topical administration, as well as additional routes of

administration are properly covered by the claim. *See*, for example, page 64, line 23 through page 65, line 20 for exemplary delivery options. As noted above, breadth of a claim is not to be equated with indefiniteness.

6. All claimed subject matter was commonly owned at all relevant times.

6a. Claims 26, 67-71 and 75-79 stand rejected as obvious over Ferrara in view of Cox. Ferrara is cited as teaching a role of VEGF in angiogenesis, and therapeutic applications of VEGF-induced angiogenesis in treatment of ischemia and other pathological conditions. The Examiner acknowledges that Ferrara does not teach modulation of VEGF by introduction of a zinc finger protein to target VEGF. Cox is cited as discussing use of zinc finger proteins to modulate endogenous genes including VEGF. The Examiner takes the view that it would have been obvious to combine the teachings of the references for the benefit of treating diseases, such as ischemia, as described by Ferrara et al. This rejection is respectfully traversed.

Ferrara reviews experiments in which a single isoform of VEGF protein (human VEGF165) is administered to a patient to induce angiogenesis. By contrast, when a zinc finger protein induces expression of an endogenous VEGF gene, all isoforms of the gene are expressed (see paragraph 5a above). The different isoforms of VEGF are known to have different roles in angiogenesis (see Grunstein et al., Mol. Cell. Biol. 20, 7282-7291 (2000), copy attached). For example, it has been reported that only VEGF164 (mouse equivalent of human VEGF165) can fully rescue tumor growth (id., see abstract). When all isoforms of VEGF are induced via administration of a zinc finger protein, it was not known that the aggregate effect of their different functions would be the same as that of the single isoform VEGF165. For example, the other isoforms might compete with VEGF165 for binding to a receptor inhibiting the effect of VEGF165. Nevertheless, the present specification provides data showing that administering a zinc finger protein and consequent induction of all isoforms of VEGF is indeed effective to stimulate angiogenesis and wound healing (see specification at pp. 98-100).

It is respectfully submitted that insufficient motivation has been identified to modify the teachings of Ferrara by replacing the administration of a single isoform of VEGF protein with a zinc finger protein. "To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or

motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance,* 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (BPAI 1993). Here, the motivation asserted by the Examiner of treating diseases such as ischemia provides reason to perform Ferrara's methods as written but not to modify them. Moreover, Ferrara's observation that the "finding that VEGF protein is able to promote therapeutic angiogenesis even at minute concentrations [citations omitted] suggests that gene therapy may not offer advantages over the recombinant protein" (p. 119, column 1, second paragraph) would have discouraged, and thereby taught away from efforts to develop alternative therapies by modulation of genes. Accordingly, it is submitted that Ferrara does not provide motivation that would have impelled the artisan to the specific combination of modulating angiogenesis using zinc finger proteins represented by the present claims.

Further, it is submitted that the combination of references would not have provided a reasonable expectation of success. As discussed above, the effect of administering a zinc finger protein and thereby inducing multiple isoforms of VEGF, each having different properties was not the equivalent of administering the isolated 165 isoform of VEGF protein. Each of the different isoforms of VEGF has unique activities, and may interact to different extents and at different points in the complex series of events leading to angiogenesis. As noted above, only VEGF165 can fully rescue tumor growth. The other isoforms might compete with VEGF165 for binding to a receptor inhibiting the effect of VEGF165, and thus not achieve effective modulation of angiogenesis. Therefore, Ferrara's results with administration of VEGF165 do not provide a reasonable expectation of success for the claimed methods.

6b. Claim 95 stands rejected as obvious over Ferrara, in view of Baird, in view of Cox. Ferrara and Cox are applied as above. However, the Examiner acknowledges the references do not teach the role of VEGF in wound healing. Baird is cited as teaching the upregulation of VEGF after hypoxia is essential for wound healing. The Examiner takes the view that it would have been obvious to combine the references for the benefit of wound healing. This rejection is respectfully traversed.

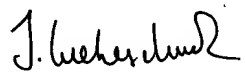
First, it is submitted that insufficient motivation has been provided to combine Baird's teaching with that of Ferrara. Baird's comments are offered to illustrate a possible mechanism for wound healing, rather than to propose a therapy. That upregulation of VEGF may be necessary for wound healing does not mean that upregulation is sufficient. Wound healing is a complex process involving many molecules. Unless upregulation of VEGF is a rate limiting step, it is not apparent that delivery of VEGF protein to stimulate aniogenesis, as proposed by Ferrara, would be effective for wound healing. The Baird reference does not attempt to address this issue. Accordingly, it is submitted that one would not have been motivated to combine the teachings of Baird and Ferrara to provide a method of administering VEGF protein to stimulate wound healing, nor would the combination of these references have provided a reasonable expectation of success.

Second, it is submitted that insufficient motivation and expectation of success has been provided to combine the teachings of Ferrara with those of Cox for essentially the same reasons as discussed in connection with claim 67. Even assuming arguendo one were to combine the teachings of Baird and Ferrara, it is not apparent why one would replace Ferrara's strategy of administering VEGF165 protein with Cox's strategy of administering a zinc finger protein to induce all isoforms of VEGF. The asserted benefit of wound healing is too general to provide motivation toward the specific combination of elements represented by claim 95. The benefit of treating wound healing could apply to administering VEGF protein, as in Ferrara, any other method of stimulating angiogenesis as well as approaches of treating wounds that are unrelated to angiogenesis. The references provide no teaching specific to administration of zinc finger proteins to stimulate angiogenesis and thereby treat wounds. Further, the observation that administration of a single isoform of VEGF can induce angiogenesis in some circumstances, does not provide a reasonable expectation of success that inducing all isoforms of VEGF via administration of a zinc finger protein would be effective in healing wounds.

For these reasons, withdrawal of the rejection is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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